



June 12, 2022

Submitted to regulations.gov Docket ID: EPA-HQ-ORD-2010-0396

Wayne Cascio,

Director, Center for Public Health & Environmental Assessment.

Re: Availability of the Draft IRIS Toxicological Review of Formaldehyde (Inhalation). 87 Fed. Reg. 22208 (April 14, 2022).

Dear Dr. Cascio:

The American Chemistry Council (ACC)¹ appreciates the opportunity to submit comments to EPA regarding the draft IRIS Toxicological Review of Formaldehyde via the inhalation route of exposure. Our comments focus on the science policy aspects of the draft Formaldehyde Review and complement the comments submitted by ACC's Formaldehyde Panel that is part of ACC's Chemical Products and Technology Division (CPTD).

Please contact Jessica Ryman-Rasmussen at 202-249-6406 or jessica_ryman-rasmussen@americanchemistry.com if you have any questions.

Sincerely,

A handwritten signature in black ink, appearing to read "Jessica Ryman-Rasmussen".

Jessica Ryman-Rasmussen, PhD, DABT
Senior Director, Chemical Management

¹ The American Chemistry Council (ACC) represents the leading companies engaged in the multibillion-dollar business of chemistry. ACC members apply the science of chemistry to make innovative products, technologies and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health, safety and security performance through Responsible Care®; common sense advocacy addressing major public policy issues; and health and environmental research and product testing. ACC members and chemistry companies are among the largest investors in research and development, and are advancing products, processes and technologies to address climate change, enhance air and water quality, and progress toward a more sustainable, circular economy.



mg/m³ formaldehyde. The NOAEL for cell proliferation is 1.25 mg/m³ for long-term exposures. Thus a threshold approach to setting a guideline for cancer effects is appropriate.

4. The systematic review methods used in the draft Formaldehyde Review need further improvements to fully address the 2011 recommendations from the NASEM and the guidance in the IRIS Handbook.

In 2011, a NASEM Committee reviewed an earlier draft IRIS assessment for formaldehyde (2011 report).⁸ The 2011 report included evaluation of the general methodology used in the assessment and provided recommendations for improvement of the assessment and the general IRIS process. Overall, the committee found that EPA's draft assessment was not prepared in a logically consistent fashion, lacked clear links to an underlying conceptual framework and did not sufficiently document methods and criteria used to identify evidence for selecting and evaluating studies. Notably, the Committee devoted a full chapter in the final NASEM report to a roadmap for revising the IRIS assessment process.

Further NASEM reviews of the IRIS Program include the 2014 review of the IRIS program (2014 report),⁹ and the 2018 review of the IRIS program (2018 report).¹⁰ Taken together, these reviews identified important areas for improvement with respect to several critical areas, including problem formulation, evaluation of study quality, and evidence integration. Perhaps the most important recommendation was for EPA to develop an IRIS Handbook to provide detailed guidance for developing IRIS assessments. In November 2020, EPA released a draft IRIS Handbook (the Handbook) for public comment and review by NASEM.¹¹ This was a long-awaited step toward meeting the NASEM recommendations for the IRIS Program and providing a transparent framework for how IRIS assessments are developed. ACC provided substantive comments on the Handbook, and we incorporate those by reference.¹²

The 2022 draft Formaldehyde Review needs further improvement to fully meet the recommendations from both the NASEM reviews and EPA's own guidance for the IRIS assessment process contained in the Handbook. We highlight several key areas below.

⁸ National Research Council. 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Washington, DC: The National Academies Press. <https://doi.org/10.17226/13142>.

⁹ National Research Council. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. <https://doi.org/10.17226/18764>.

¹⁰ National Academies of Sciences, Engineering, and Medicine. 2018. Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25086>.

¹¹ U.S. EPA. ORD Staff Handbook for Developing IRIS Assessments (Public Comment Draft, Nov 2020). U.S. EPA Office of Research and Development, Washington, DC, EPA/600/R-20/137, 2020.

¹² Docket ID EPA-HQ-ORD-2018-0654-0022.

A. Problem formulation

NASEM recommended that problem formulation should be used to focus the goals of systematic review, and should serve to organize the assessment around the scientific issues that are anticipated such as critical health endpoints, relevant information about the MOA underlying these effects, and biological plausibility.¹³ The NASEM recommendations are consistent with multiple peer-reviewed and public health agency systematic review frameworks that emphasize the importance of providing a clear research question that sets the scope of the review.^{14,15,16}

Following the 2011 NASEM recommendations, in 2012, EPA initiated the formaldehyde assessment. Phase 1 tasks – including numerous literature searches – were conducted until the draft was suspended in 2017. The draft was subsequently “unsuspended” in March 2021 and EPA continued the 2017 assessment where it had stopped. The 2022 draft Formaldehyde Review contains no discussion of problem formulation activities or an Assessment Plan. There is very little discussion of how EPA arrived at the Populations, Exposures, Comparators, and Outcomes (PECO) statements, and no discussion of EPA’s hypotheses regarding critical endpoints for formaldehyde assessment.

To meet the NASEM recommendations, EPA should have organized the draft Formaldehyde Review around plausible MOAs and/or hypotheses regarding the most critical formaldehyde effects. At a minimum, EPA should revise the draft to include discussion regarding problem formulation and scoping activities that occurred in 2012 and again in 2021, particularly considering the many changes to the IRIS Program in the 10 years between initiation of the assessment and its release.

B. Study selection and study quality assessment

Key recommendations from the various reviews of the IRIS Program emphasize the importance of providing a clear and transparent method for selection of studies and evaluation of study quality, including risk of bias and other issues.

¹³ National Research Council. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. <https://doi.org/10.17226/18764>, Chapter 3.

¹⁴Office of Health Assessment and Translation. 2019. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. OHAT, National Toxicology Program, National Institute of Environmental Health Sciences. https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookmarch2019_508.pdf

¹⁵ World Health Organization (WHO). 2021. Framework for the use of systematic review in chemical risk assessment. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

¹⁶ Schaefer HR, Myers JL. Guidelines for performing systematic reviews in the development of toxicity factors. Regul Toxicol Pharmacol. 2017 Dec;91:124-141. doi: 10.1016/j.yrtph.2017.10.008. Epub 2017 Nov 6. PMID: 29080853.

The 2022 draft Formaldehyde Review is not clear on the methods for study selection, and in some cases appears to deviate from best practices for systematic review, particularly for studies published between 2016 and 2021. Specifically, for the 2016-2021 studies, after comparing these studies to the PECO criteria, EPA assessed whether studies were “potentially impactful” – a subjective process to further narrow the body of evidence. EPA states this process relies on “expert judgment by two reviewers.”¹⁷ Particularly concerning is that aspects of study quality assessment are intertwined in these criteria – for example, the criteria pertaining to animal studies with multiple dose levels. While multiple doses are preferred to evaluate dose-response relationships in animal toxicity studies, some single-dose studies may still be informative for critical endpoints or MOAs and therefore should not be excluded before full evaluation. Additionally, criteria related to selecting relevant mechanistic data are vague, with no guidance other than inclusion of only those “most directly related to the mechanistic uncertainties identified in the 2017 draft.”¹⁸ The subjective selection of recently published studies is apparent in the failure to include numerous critical re-analyses and MOA assessments, as detailed in the comments submitted by ACC’s Formaldehyde Panel.

The study quality assessment framework used in the 2022 draft appears different from that described in the Handbook, allows for significant reviewer subjectivity, and ultimately is unclear on how confidence classifications were determined. The depiction of EPA’s evaluation of study confidence process (Figure II) is convoluted, and the study evaluation tables (e.g., Appendix Tables A-105 and A-106) that summarize results of individual studies are difficult to read and interpret.

Further, the EPA approach to study quality assessment focuses on three areas: (1) reporting quality, (2) risk of bias, and (3) study sensitivity, but primarily emphasizes risk of bias. Certain categories are more important to judging study quality than others. For example, exposure characterization is a critical evaluation domain for epidemiological studies, including the formaldehyde literature, which is plagued by studies with poor surrogates for exposure (e.g., studies relying on next of kin reporting embalming practices of deceased workers). The 2022 draft includes a lettered “grading” system for exposure assessment; this system, which is poorly described, does not appear in the Handbook or in any other agency study evaluation framework. Additionally, risk of bias is only one facet of internal validity (bias reflects a systematic error only, while internal validity is also impacted by other non-systematic errors).

For the evaluation of MOA information, EPA notes that “in general, studies relevant to mechanistic interpretations informing hazard identification were not

¹⁷ Toxicological Review of Formaldehyde (Inhalation) Supplemental Information, Appendix F, page F-5.

¹⁸ Id., Appendix F, page F-6.

individually evaluated.”¹⁹ However, the sections that follow indicate that some data were assessed for risk of bias and other domains, but with differing methods for each endpoint. For non-cancer respiratory mechanistic studies, EPA follows the general Handbook framework for rating these studies as low, medium, or high confidence. For mechanistic studies of non-cancer extra-respiratory effects, such as circulating blood cells, however, it appears no confidence evaluations were conducted, despite the fact that some of these studies have been used to inform carcinogenic hazard in the LHP malignancies (see page A-554).

Finally, for epidemiological studies of genotoxic endpoints, a third process was used, which is summarized as follows:

an overall conclusion of “no obvious bias” was used if no concerns were identified. For studies with a potential bias identified, the potential bias or issue was summarized in the comment row. For each assay (e.g., chromosomal aberrations, CBMN, Comet assay), factors related to assay methods that could affect the endpoint values were identified using published reviews from collaborations that compared assay methods across epidemiological studies (Fenech, 2020; Møller et al., 2020; Bonassi et al., 2011; Fenech et al., 2011; Valverde and Rojas, 2009; Bonassi et al., 2005).²⁰

Interestingly, on page A-222, the mechanistic epidemiological study by Zhang et al. (2010),²¹ which has been all but refuted in a number of peer-reviewed publications (see, for example, Gentry et al., 2013;²² Mundt et al., 2017²³) is discussed only briefly by EPA; the comment column simply states, “small sample numbers, no obvious bias.” The Gentry and Mundt papers are also cited, but the re-analyses presented in these studies are largely dismissed and not integrated with Zhang et al. (2010) or any of the other human studies evaluating markers of genotoxicity.

¹⁹ Id., Appendix A, page A-235.

²⁰ Id., Appendix A, page A-187.

²¹ Zhang, L., Tang, X., Rothman, N., Vermeulen, R., Ji, Z., Shen, M., Qiu, C., Guo, W., Liu, S., Reiss, B., Freeman, L. B., Ge, Y., Hubbard, A. E., Hua, M., Blair, A., Galvan, N., Ruan, X., Alter, B. P., Xin, K. X., Li, S., ... Lan, Q. (2010). Occupational exposure to formaldehyde, hematotoxicity, and leukemia-specific chromosome changes in cultured myeloid progenitor cells. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*, 19(1), 80–88. <https://doi.org/10.1158/1055-9965.EPI-09-0762>

²² Gentry, P. R., Rodricks, J. V., Turnbull, D., Bachand, A., Van Landingham, C., Shipp, A. M., Albertini, R. J., & Irons, R. (2013). Formaldehyde exposure and leukemia: critical review and reevaluation of the results from a study that is the focus for evidence of biological plausibility. *Critical reviews in toxicology*, 43(8), 661–670. <https://doi.org/10.3109/10408444.2013.818618>

²³ Mundt, K. A., Gallagher, A. E., Dell, L. D., Natelson, E. A., Boffetta, P., & Gentry, P. R. (2017). Does occupational exposure to formaldehyde cause hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells?. *Critical reviews in toxicology*, 47(7), 592–602. <https://doi.org/10.1080/10408444.2017.1301878>

Overall, EPA does not sufficiently address the NASEM recommendations relating to evaluating the quality and reliability of individual studies and must improve this in their general approach to study quality evaluation. EPA should revisit its framework for evaluating exposure assessment in epidemiological studies of formaldehyde exposure and revise its process for evaluating mechanistic information to ensure it is a uniform and reproducible methodology across endpoints. EPA should consider aligning with the exposure characterization domain within the data quality evaluation framework developed for Toxic Substances Control Act (TSCA) risk evaluations.²⁴

C. Evidence integration

NASEM has consistently recommended improvements to the evidence integration process, including its transparency. Evidence integration should focus on outcomes or endpoints with robust evidence and fully consider study quality. This should include consideration of MOA. As detailed further below, the 2022 draft does not fully meet this recommendation, particularly with respect to lymphohematopoietic malignancies. EPA concluded “evidence demonstrates” that formaldehyde inhalation causes myeloid leukemia in humans, despite the weak human evidence, lack of evidence in animal studies, and lack of a biologically plausible MOA.

Regarding evidence synthesis and integration within and across lines of evidence, the 2022 draft Formaldehyde Review does not follow best practices for systematic review. Perhaps most importantly, there is a greater reliance on “strength” rather than “weight” of evidence. For example, the draft concludes that the strength of the human evidence for myeloid leukemia is “robust” based on “several” studies with consistent findings. EPA’s conclusion is based largely on the Beane Freeman analyses of the NCI cohort (pg. 1-542). EPA did not appropriately integrate apparently conflicting findings in the older epidemiological studies (Hauptman et al. (2009)²⁵ funeral workers study, Beane Freeman et al. (2009)²⁶ analysis of the NCI cohort) with the analyses published more recently, which demonstrate no excess in cancer risk (e.g., Checkoway et al. (2015) re-analysis of the NCI cohort). EPA should re-examine its evaluations of study confidence (and risk of bias, especially including statistical analyses) and more fully integrate and

²⁴ [add citation]

²⁵ Hauptmann, M., Stewart, P. A., Lubin, J. H., Beane Freeman, L. E., Hornung, R. W., Herrick, R. F., Hoover, R. N., Fraumeni, J. F., Jr, Blair, A., & Hayes, R. B. (2009). Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. *Journal of the National Cancer Institute*, 101(24), 1696–1708. <https://doi.org/10.1093/jnci/djp416>

²⁶ Hauptmann, M., Stewart, P. A., Lubin, J. H., Beane Freeman, L. E., Hornung, R. W., Herrick, R. F., Hoover, R. N., Fraumeni, J. F., Jr, Blair, A., & Hayes, R. B. (2009). Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. *Journal of the National Cancer Institute*, 101(24), 1696–1708. <https://doi.org/10.1093/jnci/djp416>

interpret the earlier studies in the context of the broader body of more informative and updated studies.

The 2022 draft incorporates a defined methodology and detailed discussions of mechanistic and MOA information for some endpoints, but not others. The Supplemental Information details a set of criteria for judging the strength of the evidence for mechanistic events associated with non-cancer respiratory effects (Table A-64). The draft also provides evidence tables summarizing general study characteristics and findings for mechanistic studies of respiratory effects. The “utility and notes” column provides the overall confidence rating for that study; however, details on the rating are provided only for some low confidence studies.

EPA provides no criteria for its process for considering the strength of the mechanistic studies for genotoxic findings. EPA should standardize its approach to considering mechanistic and MOA studies and apply it consistently across endpoints. Mechanistic and MOA data should not be relegated to “supplemental information” but more fully integrated into the assessment beginning early in the IRIS process.

D. Toxicity value derivation

NASEM has provided several recommendations regarding the development of toxicity values, including that toxicity values should be more representative of the body of evidence, and should use formal methods for combining multiple studies. It is critical that EPA address NASEM recommendations regarding developing toxicity values to better reflect the state-of-the-science in this field and demonstrate how the systematic review process informs the development of the values.

The 2022 draft Formaldehyde Review indicates that epidemiological data are preferred for dose-response analysis and derivation of toxicity values. In many cases, the epidemiological evidence is not suitable for use in quantitative dose-response due to insufficient exposure-response information or other issues. For formaldehyde, only animal data are adequate to describe the dose-response (i.e., threshold or ‘hockey-stick’) relationship between formaldehyde and cancer, and these are limited to nasal cancer. Despite acknowledging the evidence for LHPs is of “low confidence,” EPA derives an IUR nonetheless. For specific leukemias (or other specific LHM), neither the animal toxicology nor the epidemiological evidence demonstrates a clear causal relationship and therefore deriving a slope factor or unit risk for leukemia is inappropriate.

With regard to nasal tumors, there is substantive evidence indicating these tumors are the result of cytotoxicity and regenerative proliferation. In its derivation of IURs based on animal data, EPA presents an analysis of potential threshold-like effects (i.e., an RfC based on cellular proliferation). Ultimately, however, EPA

concludes that because the formaldehyde-induced tumors could not solely be attributed to cell proliferation and that the evidence “at least in part” supported a mutagenic MOA, a linear no-threshold approach was supported. However, the existence of multiple MOAs does not preclude EPA from deriving toxicity values based on threshold-like responses. In the case of formaldehyde, if genotoxicity were to occur, it is expected only above those exposures associated with regenerative cell proliferation, as noted by the ECHA RAC Committee (2020) quoted above.

Given the robust scientific evidence that the non-genotoxic MOA predominates and would be protective of any other MOA for carcinogenicity, EPA should consider assessing formaldehyde nasal cancer potency using a threshold approach, rather than a linear, no-threshold IUR.